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Genetic markers of cardiovascular risk in patients with hand-arm vibration syndrome combined with arterial hypertension

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ABSTRACT

We investigated polymorphism of genes of endothelin I (EDN1), endothelial NO-synthase (NOS3(e)), plasminogen activator type 1 (PAI-1) in patients suffered from hand-arm vibration syndrome (HAVS), arterial hypertension (AH), and combined course of HAVS and AH. In most cases we revealed pathological variants of genes of endothelin I, endothelial NO-synthase, and plasminogen activator type 1 taking part in regulation of endothelium and systemic hemostasis function. This fact allows to consider such gene pathology as early markers of higher risk of thrombogenic and thrombophilic disorders.

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Introduction

Forming and progression of cardiovascular disorders in hand-arm vibration syndrome and arterial hypertension include a chain of pathogenic links among them microcirculatory and metabolic changes are high important, due to endothelial dysfunction and hemostasis disorders [1]. In that context the study of genes encoding proteins and taking part in regulation mechanisms of vascular tone, control of thrombocytic plasma hemostasis is of current importance that can influence the processes of vascular remodeling [2].

Polymorphic variants of genes associated with increased risk of development and progression of microhemocirculation disorders [3, 4]. For this reason investigation of genes which are responsible for endothelium and systemic hemostasis disorders will help to reveal a genetic predisposition to increased cardiovascular risk [5].

Aim of the Research

To identify polymorphic variants of genes associated with endothelial dysfunction and disorders of vascular-thrombicytic hemostasis in patients suffered from hand-arm vibration syndrome combined with arterial hypertension.

Materials and Methods

253 mail workers including 116 clincher (45.8%), 28 construction metal workers (11.1%), 109 men of working professions not having contact with noise and vibration factor (43.1%) were

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Table 1
Indicators of NOS3(e) gene polymorphism in patients of the compared groups

Indicators	Control (n = 37)		AH (n = 72)		HAVS (n = 75)		HAVS + AH (n = 69)	
	abs.	%	abs.	%	abs.	%	abs.	%
G/G	22	59.4	35	48.6*	39	52.0	33	47.8*
G/T	13	35.1	32	44.5*	31	41.4	30	43.5*
T/T	2	5.5	5	6.9*	5	6.6	6	8.7*^

* Differences are reliable in comparison with the control group ($p < 0.05$).

^ Differences are reliable in comparison with AH patients group ($p < 0.05$).

examined in conditions of the City Clinical Hospital No. 2, Novosibirsk (chief medical officer — Prof. L. A. Shpagina, MD).

Exclude criteria were acute and chronic noninfectious diseases in the exacerbation phase, clinically expressed forms of atherosclerosis, ischemic heart and brain diseases, congenital and acquired valvular diseases, and diabetes.

All examined patients were divided into four groups: 1st — 75 patients suffered from hand-arm vibration syndrome of I grade caused by local vibration, average age 47.0 ± 2.4 years, length of work with vibration 15.3 ± 1.4 years; 2nd – 69 patients suffered from HAVS of I grade caused by local vibration, in combination with AH I–II, risk 2–3, average age 47.6 ± 2.1 years, length of work with vibration 15.7 ± 1.2 years; 3rd – 72 workers not having contact with noise and vibration, with diagnose AH I–I, risk 2–3, average age 46.4 ± 2.8 years; control group — 37 people working at the same factory without contact with vibration, average age 47.5 ± 2.2 years.

The investigation was permitted by the local Ethics Committee. All patients signed a paper of informed consent for taking part in the investigation.

Examination of the patients included check-up by therapist and occupational therapist with the following examination of polymorphism of genes of endothelin I (EDN1), endothelial NO-synthase (NOS3(e)), and plasminogen activator of type 1 (PAI-1).

Isolation of DNA was carried out using phenol-chloroform extraction. Determination of polymorphic variants of PAI-1 gene was carried out by the method of revealing single nucleotide replacement in online mode with the use of competing TaqMan broaches being complementary to polymorphic DNA sites. Determination of polymorphic variants of NOS3(e) and EDN1 genes was carried out by the method of RFLP analysis.

Statistical data processing of the obtained data was carried out on the personal computer using statistical package SPSS 11.5.

Investigation of polymorphic variants of NOS3(e) showed, that G/G alleles of G894T polymorphism of gene NOS3(e) rs1799983 were determined in patients with HAVS 1.14 times rarer than in control group ($p > 0.05$). At the same time pathological polymorphic variant T/T was detected — 1.2 times more often ($p > 0.05$); polymorphic variant G/T also was determined more frequently, in comparison with control group — 1.18 times (Table 1).

Among AH patients the frequency of G/G alleles specific for health people were 1.22 times less than in control group ($p < 0.05$), at the same time pathological polymorphic variant T/T was revealed 1.25 times more often ($p < 0.05$). The least positive changes were revealed in group of patient with HAVS combined with AH: G/G alleles specific for normotensive people were determined only in 47.8% of cases, when pathological polymorphic T/T variant — in 8.7% of cases that exceeded control indicators 1.6 times ($p < 0.05$), but the same values in AH patients — 1.25 times ($p < 0.05$).

We assume that presence of T/T polymorphic variant is a risk factor of endothelial dysfunction by the reason of association with reduction of enzyme activity that lead to reduction of NO production [4, 6].

Investigation of polymorphism of G5665T gene of endothelin I (EDN1) rs5370 showed, that G/G alleles were found out in HAVS patients with the same frequency as control values (Table 2). The same changes were determined concerning pathological polymorphic T/T variant , when the number of polymorphic G/T variant exceeded control figures 1.13 times ($p > 0.05$).

The situation in the AH patient group had another directionality: frequency of G/G alleles specific for healthy people was 1.18 less ($p > 0.05$), at the same time pathological polymorphic T/T variant was registered 1.5 times more frequently ($p < 0.05$). The most negative variant of genes polymorphism was found out in patients with HAVS combined with AH: G/G alleles were revealed in 55.1% that exceeded from the control values by 1.3 times ($p < 0.05$). At the same time pathological polymorphic T/T variant was determined in 5.8 % of patients that exceeded control values 2.1 times ($p < 0.05$), the same indicators at AH patients — 1.4 times ($p < 0.05$). We have data that rs5370 (T) variant of EDN1 gene can be an additional factor in pathogenesis of atherosclerosis and ischemic

Table 2
Indicators of EDN1 gene polymorphism in patients of the compared groups

Indicators	Control (n = 37)		AH(n = 72)		HAVS (n = 75)		HAVS + AH (n = 69)	
	abs.	%	abs.	%	abs.	%	abs.	%
G/G	26	70.3	43	59.7*	50	66.7	38	55.1*
G/T	10	27.0	26	36.2*	23	30.6	30	43.5*
T/T	1	2.7	3	4.1*	2	2.7	4	5.8*^

* Differences are reliable in comparison with the control group ($p < 0.05$).
^ Differences are reliable in comparison with AH patients group ($p < 0.05$).

Table 3
Indicators of PAI-1 gene polymorphism in patients of the compared groups

Indicators	Control (n = 37)		AH(n = 72)		HAVS (n = 75)		HAVS + AH (n = 69)	
	abs.	%	abs.	%	abs.	%	abs.	%
5G/5G	9	24.3	13	18.1*	16	21.3	19	27.5*
5G/4G	19	51.4	37	51.4	40	53.3	28	40.6*
4G/4G	9	24.3	22	30.5*	19	25.4	22	31.9*^

* Differences are reliable in comparison with the control group ($p < 0.05$).
^ Differences are reliable in comparison with AH patients group ($p < 0.05$).

heart disease, because it leads to forming protein of endothelin I of higher activity [7].

By studying polymorphism of PAI-1 gene of systemic hemostasis we revealed that 5G/5G alleles of 675 5G/4G polymorphism of PAI-1 rs1799889 gene were met in the HAVS patient group 1,14 rarer than in the control group ($p > 0.05$), when pathological polymorphic 4G/4G variant was find out with the same frequency (25.4%) (Table 3).

Frequency of G/G alleles specific for healthy people in AH patients was 1.34 times lower than in the control group ($p < 0.05$), when pathological polymorphic 4G/4G variant was revealed 1.26 times more often ($p < 0.05$). Investigation of polymorphic variants of PAI-1 gene in patients with combined HAVS and AH showed that 5G/5G alleles specific for healthy people were found out in 27.5% of cases, when pathological polymorphic variant 4G/4G associated with increased risk of atherosclerosis and ischemic heart disease [8] — in 31.9% of cases, that reliably exceeded the control values by 1.3 times ($p < 0.05$) and agreed with the results in AH group.

Conclusion

Genetic set in patients suffered from hand-arm vibration syndrome combined with AH contains increased number negative polymorphic variants of genes endothelin I (EDN1), endothelial NO-synthase (NOS3(e)), activator of plasminogen of type 1 (PAI-1) associated with endothelial and hemostasiological disorders, that afford ground to consider these genes as the markers of increased risk of thrombogenic and thrombophilic complications.

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